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(54) Title: USE OF TOPIRAMATE OR DERIVATIVES THEREOF FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF POSTISCHEMIC NEURODEGENERATION

(57) Abstract

Anticonvulsant derivatives useful in treating acute ischemia-induced neurodegeneration are disclosed.

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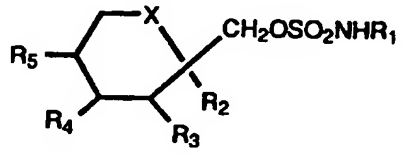
# USE OF TOPIRAMATE OR DERIVATIVES THEREOF FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF POSTISCHEMIC NEURODEGENERATION

## BACKGROUND OF THE INVENTION

Compounds of Formula I:




are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem. 30*, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. Bioorganic & Medicinal Chemistry Letters 3, 2653-2656, 1993, McComsey, D.F. and Maryanoff, B.E., J. Org. Chem. 1995). These compounds are covered by US Patent No. 4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., Epilepsia 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, Epilepsia 36 (S4) 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in Great Britain, Finland, the United States and Sweden and applications for regulatory approval are presently pending in numerous countries throughout the world.

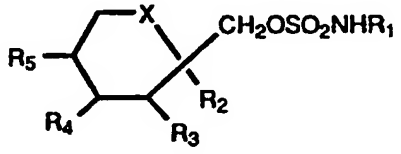
Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice

(SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., Epilepsia 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

Recent preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate should be effective in treating acute ischemia-induced neurodegeneration.

## DISCLOSURE OF THE INVENTION

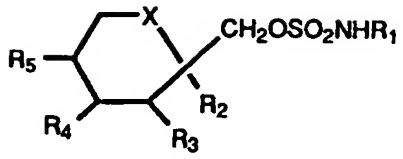
Accordingly, it has been found that compounds of the following formula I:




wherein X is O or $CH_2$, and $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ are as defined hereinafter are useful in treating acute ischemia-induced neuroprotection.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The sulfamates of the invention are of the following formula (I):

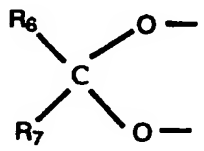



wherein

X is $CH_2$ or oxygen;

$R_1$ is hydrogen or alkyl; and

$R_2$, $R_3$, $R_4$ and $R_5$ are independently hydrogen or lower alkoxyl when X is oxygen, $R_2$ and $R_3$ and/or $R_4$ and $R_5$ together may be a methylenedioxy group of the following formula (II):




wherein

$R_6$ and $R_7$ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

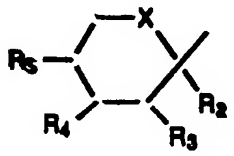
$R_1$ in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_7$ are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl.

A particular group of compounds of formula (I) are those wherein X is oxygen and both $R_2$ and $R_3$, and $R_4$ and $R_5$ together are methylenedioxy groups of the formula (II), wherein $R_6$ and $R_7$ are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where $R_6$ and $R_7$ are both alkyl such as methyl. A second group of compounds are those wherein X is $CH_2$ and $R_4$ and $R_5$ are joined to form a benzene ring. A third

group of compounds of formula (I) are those wherein both $R_2$ and $R_3$ are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula $RCH_2OH$ with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR_1$ in the presence of a base such as potassium a-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):




(b) Reaction of an alcohol of the formula $RCH_2OH$ with sulfurylchloride of the formula $SO_2Cl_2$ in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula $RCH_2OSO_2Cl$.

The chlorosulfate of the formula $RCH_2OSO_2Cl$ may then be reacted with an amine of the formula $R_1NH_2$ at a temperature of abut 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

(c) Reaction of the chlorosulfate $RCH_2OSO_2Cl$ with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M.

Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein $R_1$ is hydrogen by catalytic hydrogenation, e.g. with a noble metal and $H_2$ or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula $RCH_2OH$ may be obtained commercially or as known in the art. For example, starting materials of the formula $RCH_2OH$ wherein both $R_2$ and $R_3$, and $R_4$ and $R_5$ are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a $R_6COR_7$ ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Vol. 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula $RCH_2OH$ by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed US Patent: No.4,513,006, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of $R_2$, $R_3$, $R_4$ and $R_5$ on the 6-membered ring. Preferably, the oxygenes of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The activity of the compounds of formula I in treating acute ischemia-induced neurodegeneration was determined from the results of a study in which topiramate (dissolved in 0.1 M KCl at 33 mg/mL and diluted into isotonic saline) was found to exert a dose-related neuroprotective effect in a rat model of global (whole body) ischemia. In the study model, a transient ischemia (11 min) was induced in anesthetized rats by applying a precisely controlled pressure to the chest that was sufficient to prevent the heart from pumping blood to the brain. After the period of chest compression, resuscitation was initiated by external cardiac massage and mechanically assisted ventilation with 95% oxygen. Rats in which spontaneous ECG activity did not return within 5 min were sacrificed. Assisted ventilation was continued until persistent spontaneous ventilation occurred.

Topiramate, vehicle, or phenytoin (reference compound) was administered intravenously (i.v.), usually 30 min after resuscitation, to rats in groups 5 or 6. The compounds were administered at doses of 2.5, 5, 10, 20 or 40 mg/kg. Five days after the ischemic insult, brain damage was assessed based on a neurological examination, the incidence and severity of sound-induced seizures, motor performance on an inclined plane, exploratory behavior, and histological examination of brain tissue. A neurodeficit score, in which decrements in cranial and spinal reflexes, postural muscle tone, forepaw placing reactions, motor gait and spontaneous locomotor activity were assessed, was used to quantitate the degree of neurological impairment. Topiramate, when administered at 10 mg/kg 30 min after resuscitation, significantly reduced the neurodeficit score and seizure severity as compared to control rats. Administration of topiramate at 20 mg/kg was associated with a significantly lower neurodeficit score and significantly improved motor activity on the inclined plane as compared to control rats. Topiramate also greatly reduced neuronal cell death in the hippocampus at this dose, as determined histologically using cresyl violet-stained 10 micron sections of formalin-fixed brain tissue prepared from rats sacrificed 5 days after the ischemic insult.

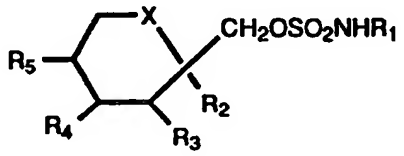
Phenytoin at 20 mg/kg iv exhibited a similar neuroprotective effect, but was more toxic than topiramate, as judged by a greater degree of neurological impairment in normal rats (e.g., higher neurodeficit score). This indicates that topiramate and phenytoin both have neuroprotective activity, but that topiramate has a greater neuroprotective index; which is similar to the higher neuroprotective index for topiramate when the anticonvulsant effects of these compounds are compared (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., Epilepsia 35 450-460, 1994).

For treating acute ischemia-induced neurodegeneration caused by stroke, head trauma, spinal unjury, non-fatal cardiac arrest, or any major surgical procedure a compound of formula (I) may be employed by administering a single i.v. dosage in the range of about 200 to 1600 mg within a period of several hours after the medical condition is identified, for an average adult human.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., i.v. Sterile injectable formulations will be prepared using appropriate solubilizing agents. A unit dose would contain about 50 to 400 mg of the active ingredient. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

WHAT IS CLAIMED IS:

1. A method for treating acute ischemia-induced neurodegeneration comprising administering to a mammal afflicted with such condition a therapeutically effective amount of a compound of the formula I:

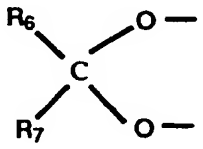



wherein

X is $CH_2$ or oxygen;

$R_1$ is hydrogen or alkyl; and

$R_2$, $R_3$, $R_4$ and $R_5$ are independently hydrogen or lower alkyl and, when X is oxygen, $R_2$ and $R_3$ and/or $R_4$ and $R_5$ together may be a methylenedioxy group of the following formula (II):




wherein

$R_6$ and $R_7$ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.

3. The method of claim 1, wherein the therapeutically effective amount is of from about 400 to 1600 mg.

4. The method of claim 1, wherein the amount is of from about 200 to 400 mg.

# INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/18 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | HARVEY L. EDMONDS ET AL.: "Topiramate as a neuroprotectant and anticonvulsant in postischemic injury" EPILEPSIA, vol. 33, no. suppl. 3, 1992, pages 118-119, XP002042704 | 1,2 |
| Y | see abstract | 3,4 |
| | --- | |
| Y | US 4 513 006 A (MARYANOFF ET AL.) 23 April 1985 cited in the application see column 1, line 15 - column 2, line 18 see column 5, line 10 - line 19 | 3,4 |
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